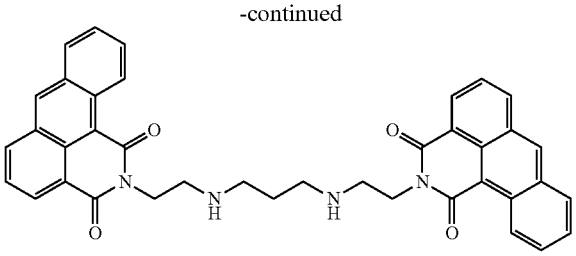
-continued



Bibenilone

[0005] Accordingly, there exists a need in the art for a naphthalimide or azonifide derivative as an anti-cancer agent having reduced dose-limiting toxicity and/or improved efficacy. The present invention provides a liposomal elinafide composition that addresses this and other such needs.

BRIEF SUMMARY OF THE INVENTION

[0006] In a first aspect, the present invention provides a liposome containing a phosphatidylcholine lipid, a sterol, a poly(ethylene glycol)-phospholipid conjugate (PEG-lipid), and elinafide. In a further aspect, less than about 20% of elinafide is released in vitro from the liposome within about 40 hours.

[0007] In a second aspect, the present invention provides a liposomal elinafide composition for the treatment of cancer. The composition includes a liposome containing a phosphatidylcholine lipid, a sterol, PEG-lipid, and elinafide, and a pharmaceutically acceptable excipient.

[0008] In a third aspect, the present invention provides a method for preparing liposomal elinafide. The method includes: a) forming a first liposome having a lipid bilayer including a phosphatidylcholine lipid and a sterol, wherein the lipid bilayer encapsulates an interior compartment or space containing an aqueous solution; b) loading the first liposome with elinafide, or a pharmaceutically acceptable salt thereof, to form a loaded liposome; and, optionally c) forming a mixture containing the loaded liposome and a PEG-lipid under conditions sufficient to allow insertion of the PEG-lipid into the lipid bilayer.

[0009] In a fourth aspect, the present invention provides a method for treating cancer comprising administering to a patient in need thereof the liposomal elinafide composition of the invention.

[0010] In a fifth aspect, the method for treating cancer has reduced side effects commonly associated with free elinafide, including muscle myopathy, myelosuppression, neuromuscular toxicity, and QTc prolongation.

BRIEF DESCRIPTION OF THE DRAWINGS

[0011] FIG. **1** shows cryo-TEMs of various elinafide liposomes. FIG. **1**A represents a cryo-TEM of example 1a shown at 52,000× magnification (scale bar: 200 nm). FIG. **1**B represents a cryo-TEM of example 1b shown at 52,000× magnification (scale bar: 200 nm). FIG. **1**C represents a cryo-TEM of example 1c shown at 52,000× magnification (scale bar: 200 nm). FIG. **1**D represents a cryo-TEM of example 1d shown at 52,000× magnification (scale bar: 200 nm).

[0012] FIG. **1**E represents a cryo-TEM of example 1e shown at 52,000× magnification (scale bar: 200 nm). FIG. **1**F represents a cryo-TEM of example 1f shown at 52,000× magnification (scale bar: 200 nm).

[0013] FIG. **2**A shows the in vitro release of elinafide from the liposome in fetal bovine serum at 37° C. over time for examples 1a, 1b, and 1c. FIG. **2**B shows the in vitro release of elinafide from the liposome in fetal bovine serum at 37° C. over time for examples 1d, 1e, and 1f.

[0014] FIG. **3**A shows the mean tumor volume of A549 human NSCLC xenografts in athymic nude mice after a single intravenous administration of saline, free elinafide, or liposomal elinafide. FIG. **3**B shows the mean tumor volume of HT29 human colorectal xenografts in athymic nude mice after a single intravenous administration of saline, free elinafide, or liposomal elinafide. FIG. **3**C shows the mean tumor volume of BxPC3 human pancreatic xenografts in athymic nude mice after a single intravenous administration of saline, free elinafide, or liposomal elinafide. All data are represented as mean f standard error of 5 to 10 mice.

[0015] FIG. **4**A shows the mean tumor volume of HT29 human colorectal xenografts in athymic nude mice after a single intravenous administration of liposomal elinafide, Abraxane, or DOXIL. FIG. **4**B shows the median survival of athymic nude mice bearing HT29 human colorectal xenografts after a single intravenous administration of liposomal elinafide, Abraxane, or DOXIL. All data are represented as mean f standard error of 5 to 10 mice.

[0016] FIG. **5**A shows the plasma concentration of elinafide over time in athymic nude mice bearing HT29 human colorectal xenograft tumors following a single intravenous administration of liposomal elinafide or free elinafide. FIG. **5**B shows the tumor concentration of elinafide over time in HT29 human colorectal xenograft tumors harvested from athymic nude mice following a single intravenous administration of liposomal elinafide or free elinafide. All data are represented as mean f standard error of 3 mice, with the exception of the 120 hr time point which contained only 2 mice in the liposomal elinafide group.

[0017] FIG. **6** shows histological sections of the quadriceps femoris of Sprague-Dawley male rats after a single intravenous administration of 50 mg/kg liposomal elinafide or 25 mg/kg elinafide. The top images are cross sections of muscle from the right leg and the bottom images are longitudinal sections of the left leg. Magnification is at 20×.

[0018] FIG. **7**A shows cryo-TEM of liposomal amonafide (sulfate) at 52,000× magnification (scale bar: 200 nm). FIG. **7**B shows cryo-TEM of liposomal amonafide (citrate) at 52,000× magnification (scale bar: 200 nm). FIG. **7**C shows cryo-TEM of liposomal UNBS-5162 (sulfate) at 52,000× magnification (scale bar: 200 nm).

[0019] FIG. **8**A shows the percent change in mean tumor volume of HT29 human colorectal xenografts in athymic nude mice after a single intravenous administration of amonafide, liposomal amonafide (citrate) or liposomal amonafide (sulfate). All data are represented as mean f standard error of 3 to 5 mice.

[0020] FIG. **9**A shows the percent change in mean tumor volume of HT29 human colorectal xenografts in athymic nude mice after a single intravenous administration of liposomal amonafide (citrate), liposomal amonafide (sulfate), azonafide, liposomal azonafide (citrate), and liposomal azonafide (sulfate). FIG. **9**B shows the percent change in mean tumor volume of HT29 human colorectal xenografts in athymic nude mice after a single intravenous administration of amonafide, liposomal amonafide (citrate), liposomal